Docket No.: CIMA 3.0-030 CONT CONT
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Pather et al.

Application No.: 09/661,693 Examiner: M. Lamm

Filed: September 14, 2000 Art Unit: 1616

For: SUBLINGUAL BUCCAL EFFERVESCENT

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Vikas Agarwal hereby declare as follows:

1. That I am Group Leader for Formulation Development at CIMA LABS Inc. (a Cephalon Company) and I have been employed by CIMA since February, 2001. That I have a Bachelor of Science from Birla Institute of Technology and Science, Pilani, India and a Ph.D. in the field of Pharmaceutical Sciences from Texas Tech University, Health Sciences Center, Amarillo, Texas conferred in 2001.

2. That my responsibilities include management, research, development and improvement of pharmaceutical delivery forms, including that which is the subject of the above-identified patent application.

3. That as part of CIMA's efforts to confirm the performance and active drug delivery characteristics of solid dosage forms containing fentanyl, I commissioned a study by

Absorption Systems, based in Exton, PA that conducts contract research for the pharmaceutical industry with a focus on ADME (an acronym for Absorption, Distribution, Metabolization, and Excretion).

4. That the study was designed to compare the mucosal permeability characteristics of tablet dosage forms according to the formulations shown in Table I attached, utilizing, in various combinations, an effervescent couple, a pH adjusting substance and the active ingredient fentanyl citrate, plus the identified, common pharmaceutical excipients.

5. That specifically, the observed data compared composition 1, containing both an effervescent couple and a pH adjusting substance with a similar composition, which contained an effervescent couple and no pH adjusting substance (designated composition 2), and a composition which contained a pH adjusting substance and no effervescent couple (designated composition 3). As noted, in each instance fentanyl was the active ingredient.

6. That the amounts of inert excipient or filler in compositions 2 and 3 were increased so that the concentration of the pH adjusting substance and effervescent couple would be at the same levels as in composition 1.

7. That an *in vitro* test method known to those skilled in the art prior to the filing date of the present application was used to evaluate permeability of the active agent, fentanyl, as described in detail in the attachment. The method utilizes cultured buccal cells, as discussed in K.L. Audus et al., "The Use of Cultured Epithelial and Endothelial Cells for Drug Transport and Metabolism Studies," Pharm. Res., 7, 5, 435-451 (1990).

8. That, the permeability data shown in the table and illustrated in the attached figure clearly demonstrate that the claimed composition results in significantly superior performance compared to compositions in which only an effervescent couple or only a pH adjusting substance is present. Specifically, the permeability value obtained using formula 1 is more than 410% greater than that of formula 2 (effervescent couple only), and more than 511% greater than that of formula 3 (pH adjusting substance only).

9. That I conclude that these data confirm that a composition including both an effervescent couple and a basic pH adjusting substance results in significantly enhanced permeability of fentanyl across a mucosal membrane.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that any such willful false statements may jeopardize the validity of this application or any patent issuing therefrom.

Signed this 20th day of April, 2006

Vikas Agarwal

Table
Test Compositions (wt%)

Component	Function	1 Effervescence + pH	2 Effervescence Only	3 pH Only
Fentanyl Citrate	Active	0.628	0.628	0.628
Mannitol	Filler	47.872	57.872	83.872
Disintegrant	Disintegrant	3.000	3.000	3.000
Sodium Bicarbonate	Effervescent component	21.000	21.000	-
Citric Acid	Effervescent Component	15.000	15.00	-
Sodium Carbonate	pH Adjusting Substance	10.000	-	10.000
Magnesium Stearate	Lubricant	2.000	2.000	2.000
Pigment	Color	0.500	0.500	0.500
Test Results Mean (std. deviation)				
Fentanyl Permeability, P_{app} (x 10^{-6} cm/sec)		95.6 (3.1)	23.3 (4.1)	18.7 (2.6)

Determination of Average Apparent Permeability (*In vitro* Test Method)

Experimental Procedure

Materials

Krebs Ringer Bicarbonate (KRB) buffer was obtained from Sigma-Aldrich (St. Louis, MO). HEPES zwitterionic buffer solution was purchased from Invitrogen (Grand Island, NY). The reservoir buffer consisted of filtered KRB buffer containing 10 mM HEPES and 0.015 mM sodium bicarbonate at pH 7.0. Tablets according to the formulations shown in the above table were prepared by direct compression using a standard rotary press. Tablet weight for each of the tablets was 200 mg, corresponding to a 5/16 inch (0.794 cm)

size. EpiOral® cells used for the permeability tests are described below.

Permeation Study through EpiOral Cell Line

EpiOral® cells plated in 6 well plates and accompanying buffer solutions for donor and receiver chambers were obtained from MatTek Corporation (Ashland, MA; a detailed product description is available at www.mattek.com). The permeation experiment was done according to instructions from the manufacturer on the second day of cell arrival. Donor buffer consisted of Dulbeccos' Phosphate Buffered Saline (DPBS) without Ca and Mg chloride, pH 7.0. The receiver buffer consisted of Dulbeccos' Phosphate Buffered Saline without Ca and Mg Chloride, pH 7.4, with 1 % BSA added to improve fentanyl recovery from the apparatus.

The receiver chamber was filled with 1 mL buffer while the donor chamber was filled with 2 mL buffer. The donor buffer was applied in 0.5 mL increments/1 min for a total volume of 2 mL. At time zero, 50 µL of the donor solution was sampled. At the end of the experiment, the complete donor content was collected at 150 minutes (or 120 minutes in experiments on the second batch of cells). Receiver samples (200 µL) were collected at 0, 30, 60, 90, 120 and 150 minutes and replaced with an equal volume of fresh receiver buffer (or at 0, 15, 30, 60, 90 and 120 minutes on second batch of cells). Fentanyl permeation was tested by application of the tablet formulations. Tests were run in triplicate.

Sample Analysis

Fentanyl was measured by LC/MS/MS using electrospray ionization.

Data Analysis

Cumulative concentrations in the receiver chamber were calculated, compensating for the removal and replacement of the 0.2 mL (200 µL) sample, as follows.

$$C_r = C^n + (0.2\ mL / 1.0\ mL) \times C^{n-1}$$

where,

C_r = the cumulative concentration in the receiver chamber
C^n = the measured receiver concentration at time point, n
C^{n-1} = the measured receiver concentration at the previous time point, n-1

The apparent permeability coefficient, P_{app}, was calculated as follows:

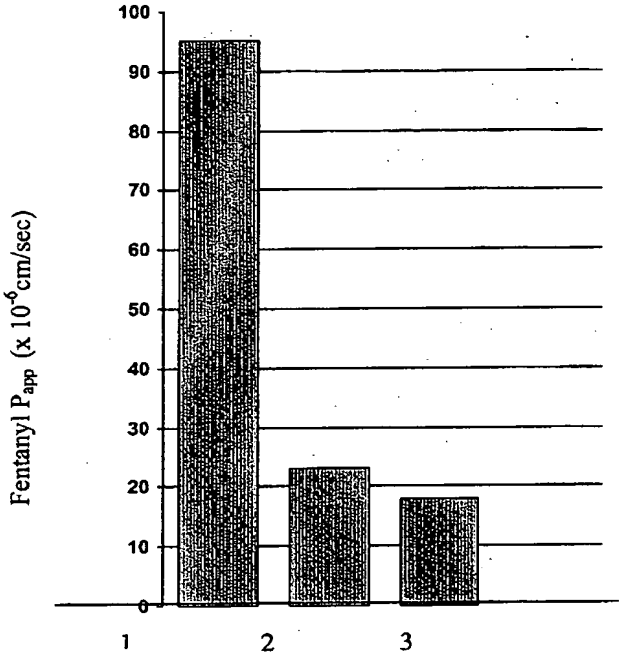
$$P_{app} = (dC_r / dt) \times V_r / (A \times C_0)$$

where,

dC_r/dt = the slope of the cumulative concentration in the receiver chamber versus time
V_r = the volume of the receiver chamber (1.0 mL)
A = the surface area of buccal epithelium available for permeation (4.2 cm^2)
C_0 = the initial concentration of compound in the donor chamber

Figure

Average apparent Permeability (P_{app}) ± STD (N=3) of Fentanyl Applied in Different Dosing Forms *In Vitro*



Treatments (Tablets)

1 - Effervescent couple + pH adjusting substance
2 - Effervescent couple only
3 - pH adjusting substance only